Multivariate statistical modelling of the pharmaceutical process of wet granulation and tableting

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Chapter 5

Optimisation of the composition and production of mannitol/microcrystalline cellulose tablets

Mixtures of mannitol and microcrystalline cellulose (MCC) were investigated on small-production scale by granulation in a high-shear mixer and compression into tablets. For both excipients only a few cases of incompatibilities with active ingredients are known. Tablets with only MCC as the filler excipient have inferior strength as compared to pure mannitol tablets, whereas disintegration time of mannitol tablets is inferior to pure MCC tablets. However, combination of both excipients resulted in sufficiently rapid disintegrating tablets with acceptable strength. The composition of the tablet mixture and the process of tablet manufacturing were optimised using statistical techniques. Next to the effects of the amounts of MCC and hydroxypropylcellulose (HPC) in the composition, the effects of the amount of water and the granulation time were evaluated. For the production of tablets both the effects of moisture content in the granules and compression force were studied. Simultaneous optimisation of crushing strength, disintegration time and ejection force of the tablets was carried out to find optimal regions in the design space for these tablet properties.

In conclusion, mannitol/MCC mixtures can be considered as an interesting alternative in case classical excipients cannot be selected in formulation development, due to chemical incompatibilities with active ingredients or inferior physical characteristics.

Introduction

Wet granulation is a process of size enlargement and is generally applied in the pharmaceutical industry to prepare powdered materials for capsules and tablets.

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Several strategies have been used to optimise the process of granulation and tablet manufacturing [1-7]. Most of the research on granulation in high-shear mixers has been performed with lactose and calcium-hydrogen-phosphate as the major filler excipients in the blend. Both calciumphosphate and lactose formulations can give rise to physical and chemical problems, the latter particularly in formulations with drugs that give the Maillard decomposition reaction. Both MCC and mannitol are relatively inert and only a few cases of incompatibilities with active ingredients have been reported.

The aim of this study was to evaluate the applicability of mannitol/MCC mixtures and to optimise the composition and production of the tablets for their granulating and tableting properties using statistical optimisation techniques.

Methods

Design of experiments

The design of experiments in this study was divided into three steps: the screening of important process variables, the robustness of the process and the final experimental design. The final design was restricted to 40 granulation experiments aimed to give quantitative information about the effect of only six process or composition variables on the granule and tablet responses.

An extensive list of all variables that affect the process of wet granulation and tableting is based on everyday experience. From this list some variables were chosen for further research, others were kept constant at a specified level. The following criteria were used to come to a selection of important variables: known for its high influence, traditionally varied to solve technological problems, easy to control and vary, meets peoples interests, affects nearly all responses. Screening experiments finally resulted in the selection of six variables and their valid ranges.

An essential step in the optimisation process is to establish the robustness (reproducibility) of the manufacture of granules and tablets against disturbances in variables that are assumed to stay constant. If the process is not robust, effects of process variables are more difficult to detect.

The six chosen process and composition variables were set at specific levels for the final experimental design. Because of the expected curvature in the response surfaces, each variable was varied at three levels. A Box-Behnken design was selected, which only needed 55 experiments [8]. Figure 1 shows a three variable Box Behnken design. No experiments at the vertices of the cubic region are necessary. This can be advantageous because the corners of the cube represent extreme combinations of factors at the edge of the experimental region where physical-chemical problems may arise.

The six variable Box Behnken design used, is shown in Table 1. The ±1 stands for the high and low level of the specific variable, and 0 stands for the medium level.

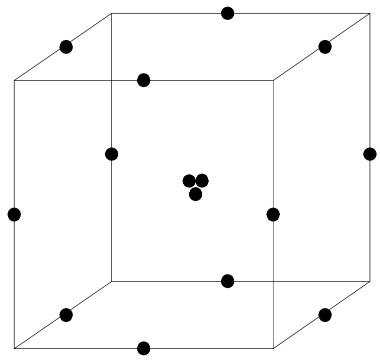

Figure 1: A three variable Box Behnken design. Each variable is varied on three levels. No experiments are selected at the corner points. The centre point is repeated several times.

The number of batches in each row that have to be granulated is given in the last column. Two of the four process variables, compression force and moisture in the granules, are not applied at the production of the granulation. These process variables can be varied using the same batch of granules. Therefore, the number of batches can be diminished from 55 to only 33 batches. Table 2 shows the variables and levels that were set. Two composition variables are varied, the amount of MCC and HPC in the blend. The other four variables: the amount of water added to the mixture, granulation time, moisture level of the granules and compression force (F_{up}), define the process. The moisture level of the granulation was set to a specific value using methods including drying in a Kocken vacuum stove. The binary mixture of MCC and mannitol can be represented by only one variable. The calculated effect of MCC, therefore, is not from the pure component. It points out the effect of the combination of MCC and mannitol.

Previous experiments showed that a high water level was incompatible with a low amount of MCC as was a low level of water with a high amount of MCC. For this reason the amount of water was set dependent on the amount of MCC according to a previous defined experimental relation given in Table 2.

Table 1: Box-Behnken design with four process: water, time, moisture and compression force (Fup), and two composition variables: MCC and HPC.

MCC	HPC	Water	Time	Moisture	Fup	# batches
±1	±1	0	±1	0	0	8
0	±1	±1	0	±1	0	4
0	0	±1	±1	0	±1	4
±1	0	0	±1	±1	0	4
0	±1	0	0	±1	±1	2
±1	0	±1	0	0	±1	4
0	0	0	0	0	0	7

Table 2 The levels of the variables in the Box-Behnken design.

Process variables	low level	medium level	high level
MCC (%)	65	75	90
Water (ml)	110+4.5*MCC	110+5.3*MCC	110+6.0*MCC
HPC (%)	2	3	5
Time (min.)	3	5	7
Moisture (%)	3	4	5
Fup (kN)	10	20	30

Statistical analysis of the results.

The use of regression analysis in this study has two main reasons, process investigation and optimisation of tablet properties. To obtain regression models that describe the data well and give good predictions, a well-defined strategy is followed. The strategy is divided into three steps.

- Outlier selection
- Model selection
- Model evaluation

The data measured are modelled to a linear model with linear, quadratic and interaction terms. The complete model is defined as follows:

$$\mathbf{y} = a + b_1\mathbf{X}_1 + ... + b_6\mathbf{X}_6 + c_1\mathbf{X}_1^2 + ... + c_6\mathbf{X}_6^2 + d_{12}\mathbf{X}_1\mathbf{X}_2 + ... + d_{56}\mathbf{X}_5\mathbf{X}_6$$

In this model the intercept *a* gives the response value **y** in the centre of the design where all variables $\mathbf{X}_1..\mathbf{X}_6$ are set to zero. The parameters *b*, *c* and *d* are regression coefficients for the linear, quadratic and two-factor interaction terms respectively.

Outlier selection

The residuals of the complete model are examined for outliers with an envelope plot of the Studentized residuals. Studentized residuals have mean zero and unit variance and they are corrected for the influence of the position in the design [9]. The residuals are plotted in an envelope plot [10]. When residuals fall outside the envelope, they are removed as outliers.

Model selection

Model selection starts with the determination of the complexity of the model. The successive addition of the linear, quadratic and interaction terms is evaluated with a F-test. The adjusted correlation coefficient ($R^2_{adj.}$) and Amemiya's prediction criterium (PRC) are calculated for these models [11]. $R^2_{adj.}$ gives the variance in the data accounted for by the regression model. The PRC compares mean squared errors of the models. Both are corrected for the number of observations and parameters in the model. For a good model, $R^2_{adj.}$ is close to 1 and PRC is as low as possible.

Variable selection is carried out to use only those variables that influence the response. The models are stripped one group at the time. Groups of a specific variable are formed by its linear and quadratic term and all interaction terms. Groups are stripped until they all are significant at the 0.05 level. The p-value shows the significance for the F-test for the mean square of the type II sum of squares explained by the group and the mean square of the residuals [12]. In the evaluation of the models $R^2_{adj.}$ and PRC are included. The model with optimal $R^2_{adj.}$ and PRC values will be chosen as the final model. However, the figures may be ambiguous. They are not always both optimal for the same model. When this is the case, selection of the final model has to be made on additional arguments. The final model was tested for lack of fit [9].

Model evaluation

After estimation of all parameters in the model, several plots of responses against process variables can be drawn and evaluated. From these plots, optimal combinations of the process variables can be found for the tablet responses to meet given criteria. For prediction properties, the square root of the leave one out squared prediction errors (RMPRESS) is calculated. If the RMPRESS, the root mean squared error (RMSE) of the model and the experimental error (s) of the centre point are of comparable size, the model can predict new response values with the same precision as described by the data.

In the process of tablet making, a number of demands have to be satisfied. Usually, optimal values for different responses are not obtained at the same settings of the process and composition variables. Overlay contour plots can be drawn for several responses in the experimental space, to find regions in the experimental space that fulfil restrictions of tablet properties.

Experimental

Granulation and compression process

Granulations were prepared according to the formulation in Table 3. MCC (Avicel PH102; Roquette) and mannitol (FMC cooperation) were mixed for 1 minute in a Gral 10 high-shear granulator (Collette) at impeller speed 650 rpm. The HPC (Aqualon) solution was added in the middle of the powder bed with the necessary amount of water. The mass was granulated for 3, 5 or 7 minutes at impeller speed 650 rpm. and chopper speed 3000 rpm. After granulation, the mass was dried in a Kocken vacuum stove at 40 ^{o}C and -1000 mbar vacuum. The moisture content of the granules was determined with a Sartorius IR humidity analyser. The granules were sieved through a 710 µm sieve on an Erweka AMD oscillator. From the granules 400 g was taken and admixed with 1.5% colloidal silicon dioxide (Defussa) during 1 minute followed by admixing with 0.5% magnesium stearate (Otto Breyer b.v.) during 1 minute in an Erweka mixer. After admixing, the granules were compressed into flat

Table 3 The formulation of the tablets.

HPC	2-3-5%
magnesium stearate	0.5%
colloidal silicium dioxide	1.5%
MCC + mannitol	ad. 100%

faced tablets (9.0 mm; 250 mg) at a compression force of 10, 20 or 30 kN on a HOKO KJ excenter press.

Granule and tablet properties

Before admixing the granules with colloidal silicon dioxide and magnesium stearate, the particle size distribution was measured by sieve analysis (Retsch 50 Hz, 20 min. sieves 600, 500, 355, 212, 125, 75 µm), and the median diameter of the granules (D_{50}) was calculated. The flow rate of 100 g of granules through a funnel with an orifice of 4.5 mm was measured as were the poured and tapped specific volumes. During tableting, ejection forces of the tablets were registered with a Siemens Oscilloreg. Thirty minutes after preparation, crushing strengths of 10 tablets were measured on a Roche HT 300. Disintegration times of six tablets were measured with disks according to USP XXII.

The selected Box-Behnken design needed 55 experiments. Table 4 shows settings of the process and composition variables according to the BB design and the measured crushing strength (CS), disintegration time (DT) and ejection force (EF) of the tablets. Table 5 shows the measured granule properties. A-C=Flow through funnel with orifice 4.5, 6.0 and 9.0 mm respectively (s), D, E=poured and tapped volumes ($ml.g^{-1}$), F=Carr's index, G=median granule size (D_{50}; µm) and H-N=sieve fractions >600, 600-500, 500-355, 355-212, 212-125, 125-75, <75 (%). From experiment 14 and 15 no tablets could be obtained because of the bad compression characteristics of the granules.

Results and discussion

Robustness experiments showed that the process of wet granulation and tablet making is in control. The reproducibility of the tablet responses was considered good enough to continue the study.

Tablet properties

Tablets were compressed from the granules. One granulation experiment (90% MCC, 3% HPC, 585g H_2O, 4% moisture, granulation time 7 min.) turned out to have extremely poor compressibility properties. This batch was supposed to be tableted at two different compression forces. No tablet properties could be obtained for these experiments. Table 6 shows the results of the models for the tablet responses.

Table 4: Experimental design and measured tablet properties crushing strength (CS), disintegration time (DT) and ejection force (EF).

Nr	MCC(%)	HPC(%)	water(ml)	time(min.)	moist.(%)	comp. (kN)	CS(N)	DT(s)	EF(N)
1	75	3	500	5	3.9	20	23	11	138
2	75	3	500	5	4.3	20	48	42	110
3	75	3	510	5	4.0	20	33	24	91
4	75	3	510	5	4.3	20	38	23	91
5	75	3	510	5	3.8	20	25	11	111
6	75	3	510	5	3.8	20	35	30	92
7	75	3	510	5	3.8	20	38	34	100
8	65	3	450	7	3.8	30	55	104	126
9	65	3	450	7	3.8	10	15	2	101
10	90	3	585	3	4.0	30	11	10	50
11	90	3	585	3	4.0	10	4	2	59
12	65	3	450	3	4.2	10	23	10	235
13	65	3	450	3	4.2	30	66	291	274
14	90	3	585	7	3.7	10	*	*	*
15	90	3	585	7	3.7	30	*	*	*
16	75	5	450	5	4.0	10	14	2	99
17	75	5	450	5	4.0	30	51	138	120
18	75	5	560	5	3.8	10	17	5	74
19	75	5	560	5	3.8	30	53	400	83
20	75	2	450	5	4.2	30	75	215	358
21	75	2	450	5	4.2	10	30	2	214
22	75	2	560	5	4.0	30	51	84	99
23	75	2	560	5	4.0	10	20	6	86
24	90	3	510	5	3.3	20	22	16	81
25	90	3	510	5	4.8	20	22	15	72
26	65	3	500	5	4.8	20	61	149	117
27	65	3	500	5	3.2	20	48	65	132
28	65	3	400	5	3.1	20	44	28	141
29	65	3	400	5	4.9	20	58	72	134
30	90	3	650	5	3.4	20	6	8	53
31	90	3	650	5	5.4	20	8	15	41
32	65	2	450	7	4.0	20	49	26	153
33	65	2	450	3	4.0	20	52	42	142
34	90	2	585	7	4.4	20	9	2	68
35	90	2	585	3	4.3	20	13	4	62
36	65	5	450	3	4.0	20	37	55	138
37	65	5	450	7	4.0	20	31	32	115
38	90	5	585	7	4.2	20	6	10	44
39	90	5	585	3	4.3	20	8	16	51
40	75	3	560	7	4.5	20	65	118	79
41	75	3	560	7	3.1	20	55	54	86
42	75	3	560	3	4.6	20	57	90	88
43	75	3	560	3	3.0	20	51	33	134
44	75	3	450	3	3.0	20	51	51	134
45	75	3	450	3	4.6	20	51	38	110
46	75	3	450	7	3.1	20	43	21	127
47	75	3	450	7	4.6	20	48	47	120
48	75	2	510	5	4.8	10	22	6	92
49	75	2	510	5	4.8	30	60	125	102
50	75	2	510	5	2.8	10	11	4	91
51	75	2	510	5	2.8	30	61	48	124
52	75	5	510	5	3.1	30	57	156	110
53	75	5	510	5	3.1	10	13	6	92
54	75	5	510	5	4.5	10	23	9	85
55	75	5	510	5	4.5	30	68	421	91

Table 5: Measured physical granule properties of experiments given in Table 4. A-C=Flow through funnel with orifice 4.5, 6.0 and 9.0 mm (s), D-E=poured, tapped volumes (ml.g^{-1}), F=Carr's index, G=median granule size (D_{50}; µm), H-N=sieve fractions >600, 600-500, 500-355, 355-212, 212-125, 125-75, <75 (%).

Nr	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1	1.15	2.54	7.28	1.55	1.46	6.2	344	3.9	11.6	31.4	43.2	7.9	1.2	1.0
2	1.14	2.51	6.76	1.71	1.54	11.0	257	6.2	6.5	11.3	37.2	35.2	2.0	1.2
3	1.13	2.55	7.25	1.57	1.45	8.3	378	7.3	16.7	30.9	36.4	6.3	1.2	1.2
4	1.05	2.36	6.45	1.71	1.59	7.5	325	5.0	10.0	25.6	46.2	8.6	1.6	3.0
5	1.05	2.44	6.90	1.56	1.38	13.0	429	10.6	21.0	37.5	25.8	3.5	0.8	0.7
6	1.05	2.23	6.45	1.65	1.53	7.8	444	10.2	21.8	39.2	21.2	4.3	1.4	1.8
7	1.02	2.34	6.37	1.78	1.58	12.7	280	1.2	4.0	16.2	53.4	19.6	2.8	2.2
8	1.22	2.72	7.37	1.52	1.45	4.8	337	2.9	11.0	30.1	44.9	8.2	1.4	1.2
9	1.22	2.72	7.37	1.52	1.45	4.8	337	2.9	11.0	30.1	44.9	8.2	1.4	1.2
10	1.16	2.70	7.53	1.47	1.32	11.4	304	6.0	9.6	21.0	38.5	19.1	3.5	2.7
11	1.16	2.70	7.53	1.47	1.32	11.4	304	6.0	9.6	21.0	38.5	19.1	3.5	2.7
12	1.13	2.54	6.90	1.66	1.57	5.7	285	5.3	7.2	16.2	42.5	26.4	1.3	0.5
13	1.13	2.54	6.90	1.66	1.57	5.7	285	5.3	7.2	16.2	42.5	26.4	1.3	0.5
14	1.23	2.68	7.82	1.35	1.27	6.3	478	20.6	24.3	39.1	14.4	2.1	0.5	0.2
15	1.23	2.68	7.82	1.35	1.27	6.3	478	20.6	24.3	39.1	14.4	2.1	0.5	0.2
16	1.01	2.25	6.41	1.69	1.54	9.7	273	5.9	7.8	16.4	34.3	31.1	3.6	0.6
17	1.01	2.25	6.41	1.69	1.54	9.7	273	5.9	7.8	16.4	34.3	31.1	3.6	0.6
18	0.95	2.15	6.26	1.60	1.50	6.7	507	26.1	25.6	24.5	13.8	5.2	1.8	2.9
19	0.95	2.15	6.26	1.60	1.50	6.7	507	26.1	25.6	24.5	13.8	5.2	1.8	2.9
20	1.20	2.56	6.41	1.75	1.56	12.2	151	3.3	3.4	4.7	10.0	41.5	30.7	6.8
21	1.20	2.56	6.41	1.75	1.56	12.2	151	3.3	3.4	4.7	10.0	41.5	30.7	6.8
22	0.95	2.14	6.24	1.63	1.52	7.2	533	27.5	32.8	27.7	9.0	1.6	0.3	0.7
23	0.95	2.14	6.24	1.63	1.52	7.2	533	27.5	32.8	27.7	9.0	1.6	0.3	0.7
24	1.27	2.75	7.18	1.63	1.45	12.4	196	4.2	9.8	12.2	17.8	34.6	18.0	3.6
25	1.29	2.82	7.35	1.59	1.42	12.0	189	4.0	8.0	10.6	17.0	40.8	17.0	3.2
26	0.95	2.18	6.26	1.66	1.48	12.2	510	22.2	30.4	25.6	13.8	4.6	1.4	1.6
27	0.98	2.23	6.41	1.64	1.47	11.6	507	22.8	29.8	26.2	14.0	4.6	1.4	1.6
28	1.26	2.62	6.67	1.70	1.49	14.1	177	1.6	4.6	8.8	17.0	45.2	18.8	4.2
29	1.18	2.56	6.66	1.74	1.55	12.2	184	1.4	5.2	9.8	18.0	47.2	14.2	3.8
30	1.11	2.54	7.30	1.37	1.30	5.4	563	41.8	21.0	19.4	11.0	4.0	1.2	1.2
31	1.18	2.62	7.69	1.36	1.26	7.9	539	36.0	22.6	21.6	12.6	4.4	1.2	1.4
32	1.15	2.47	6.42	1.80	1.62	11.1	174	1.3	4.5	7.0	11.8	58.9	13.4	3.2
33	1.15	2.47	6.17	1.82	1.64	11.0	177	0.8	3.4	5.8	15.4	57.9	11.2	4.2
34	1.38	3.07	8.27	1.50	1.33	12.8	204	1.7	3.9	8.8	29.7	49.7	3.7	1.0
35	1.25	2.75	7.42	1.59	1.44	10.4	212	1.9	5.4	11.8	30.6	44.3	4.4	1.3
36	1.12	2.54	7.13	1.50	1.38	8.7	380	7.5	18.3	28.8	32.9	10.0	1.4	0.8
37	1.05	2.44	7.12	1.52	1.35	12.6	475	18.7	25.5	31.1	17.6	5.1	1.1	0.5
38	1.13	2.61	7.58	1.40	1.27	9.3	502	22.8	27.7	23.3	14.9	7.6	2.2	1.5
39	0.99	2.31	6.82	1.52	1.40	8.6	520	25.3	30.4	27.9	13.9	1.8	0.2	0.2
40	0.82	1.90	5.56	1.74	1.63	6.7	518	25.2	29.6	22.8	12.8	5.4	2.0	1.8
41	0.85	1.94	5.59	1.74	1.62	7.4	529	26.4	32.6	22.0	11.0	4.2	1.4	1.8
42	0.86	1.96	5.71	1.75	1.63	7.4	511	22.6	30.8	24.2	12.8	5.4	2.2	2.0
43	0.88	2.05	5.88	1.75	1.60	9.4	509	23.6	29.2	25.6	13.0	4.8	1.8	2.2
44	1.09	2.30	5.88	1.86	1.66	12.0	164	1.2	4.8	8.2	16.2	38.4	25.6	7.0
45	1.09	2.31	6.10	1.79	1.59	12.6	181	1.6	6.0	10.2	17.2	40.2	18.6	5.4
46	1.07	2.24	5.85	1.87	1.65	12.7	183	1.4	4.8	8.8	16.8	49.6	15.0	2.0
47	1.04	2.25	5.75	1.91	1.70	12.4	183	1.4	5.4	9.2	17.4	51.6	11.6	4.2
48	1.02	2.32	6.37	1.80	1.63	10.4	290	1.8	5.8	18.0	53.0	16.4	2.4	2.2
49	1.02	2.32	6.37	1.80	1.63	10.4	290	1.8	5.8	18.0	53.0	16.4	2.4	2.2
50	1.03	2.31	6.39	1.83	1.61	13.7	282	1.2	4.4	16.8	55.0	17.8	2.6	1.6
51	1.03	2.31	6.39	1.83	1.61	13.7	282	1.2	4.4	16.8	55.0	17.8	2.6	1.6
52	0.91	2.11	6.17	1.67	1.56	7.1	501	21.8	28.6	26.8	14.4	5.2	1.6	1.8
53	0.91	2.11	6.17	1.67	1.56	7.1	501	21.8	28.6	26.8	14.4	5.2	1.6	1.8
54	0.88	2.04	5.82	1.72	1.60	7.5	516	23.2	31.8	24.8	12.6	4.4	1.4	1.8
55	0.88	2.04	5.82	1.72	1.60	7.5	516	23.2	31.8	24.8	12.6	4.4	1.4	1.8

Table 6: Final models for the ejection force, crushing strength and disintegration time of mannitol MCC tablets. Outliers, R^2, and lack of fit probability are given. Further model parameters are given with their significance (* p<0.05, ** p<0.01, *** p<0.001), and RMSE, error of reproduction (s) and RMPRESS values. t1 and t2 give indications of properties for the tablets with bad compression properties.

Response	Ejection force (N)		Crushing strength (N)		Disintegration time (s)	
Outliers	4		-		-	
R^2	0.85		0.93		0.91	
p(Lack of fit)	0.97		0.75		0.69	
Intercept	98.8		3.3794		3.22	
MCC	-28.0	***	-0.4785	***	-0.658	***
Fup	7.0	**	0.5741	***	1.687	***
moisture	-8.8	**	0.1555	**	0.489	***
HPC					0.231	***
water	-11.0	***	-0.0341		0.278	**
MCC^2			-0.3472	***	-0.241	**
Fup^2	-9.8	**	-0.2358	***	-0.315	*
$moisture^2$			0.1225		0.527	**
$water^2$			0.2002	***	0.315	**
MCC*Fup					-0.378	*
MCC*moisture					-0.357	*
MCC*HPC					0.158	*
MCC*water			-0.2660	***	-0.288	*
Fup*moisture			-0.1842	*		
RMSE	12		0.22		0.48	
s	17		0.26		0.53	
RMPRESS	12		0.25		0.55	
	t1: 43 N t2: 57 N		t1: 3 N t2: 10 N		t1: 1 s t2: 13 s	

Disintegration time

The analysis of the results of the disintegration time will be used to show the statistical route mentioned earlier in this chapter and is shown in detail. A logarithmic transformation was used to correct for the heteroscedastic measurement error of the disintegration time. No outliers were removed.

Scheme 1 shows the detailed results of the model building. A complete model with linear, quadratic and interaction terms was selected to fit the disintegration time data. A variable selection was carried out on this model. The granulation time variable group provides no significant addition to the model (p=0.3969). The whole variable group was removed. The new complete model shows no insignificant variable groups (p<0.05). The second model has an improved PRC, but $R^2_{adj.}$ decreased a little. Comparing both models the second was selected because it is simpler than the first model. Looking to the model in detail, only the MCC group of interactions is significant (p-values PROB>|T| below 0.05). The other interactions were removed from the model as was the quadratic HPC term (p=0.25). The final

Scheme 1: Detailed results of the modelling of the logarithmic scaled disintegration time.

ln disintegration time

Regressors	R2	F	p	R2adj	PRC
linear	0.8026	66.302	0.0000	0.7768	0.5149
quadratic	0.0801	6.619	0.0003	0.8475	0.3870
cross	0.0669	2.209	0.0385	0.8951	0.3267
TOTAL	0.9496	17.432	0.0000		

full model

Factor	SSII	MS	F	p	
MCC	25.4282	3.6326	16.9917	0.0000	R2 = 0.9496
water	5.3801	0.7686	3.5951	0.0082	PRC = 0.3267
time	1.6371	0.2339	1.0939	0.3969	R2adj = 0.8951
Fup	67.3874	9.6268	45.0296	0.0000	LOF = 0.7491
moisture	4.8328	0.6904	3.2294	0.0140	
HPC	5.3739	0.7677	3.5909	0.0082	

full model (-time)

Factor	SSII	MS	F	p	
MCC	25.3155	4.2192	19.3384	0.0000	R2 = 0.9341
water	4.8740	0.8123	3.7232	0.0064	PRC = 0.3046
Fup	67.1179	11.1863	51.2711	0.0000	R2adj = 0.8929
moisture	4.9530	0.8255	3.7836	0.0058	LOF = 0.7341
HPC	5.3972	0.8995	4.1229	0.0035	

ANALYSIS OF VARIANCE

SOURCE	DF	SS	MS	F-value	PROB>F
MODEL	20	98.9851	4.94925	22.6843	0.0000
ERROR	32	6.98175	0.21818		
TOTAL	52	105.967			

RMSE = 0.46710 PRESS = 21.33245

VARIABLE	PARAMETER ESTIMATE	STANDARD ERROR	T FOR H0: PARAMETER=0	PROB>|T|
intercept	3.2160	0.06416	50.12450	0.0000
MCC	-0.6482	0.09878	-6.56183	0.0000
water	0.2556	0.09386	2.72311	0.0052
Fup	1.6419	0.10439	15.72798	0.0000
moisture	0.4919	0.11846	4.15281	0.0001
HPC	0.2965	0.11008	2.69323	0.0056
MCC^2	-0.2515	0.09320	-2.69855	0.0055
$water^2$	0.3065	0.12420	2.46788	0.0096
Fup^2	-0.2671	0.15280	-1.74833	0.0450
$moisture^2$	0.4960	0.17399	2.85049	0.0038
HPC^2	-0.0523	0.07685	-0.68069	0.2505
MCC*water	-0.2896	0.12113	-2.39099	0.0114
MCC*Fup	-0.3767	0.16076	-2.34306	0.0128
MCC*mois.	-0.3550	0.15626	-2.27170	0.0150
MCC*HPC	0.1493	0.08598	1.73599	0.0462
water*Fup	-0.2138	0.15835	-1.35010	0.0932
water*mois.	0.0977	0.13306	0.73414	0.2341
water*HPC	0.1594	0.10233	1.55816	0.0645
Fup*mois.	0.1670	0.18567	0.89956	0.1875
Fup*HPC	0.1450	0.07703	1.88236	0.0345
mois.*HPC	0.0439	0.13134	0.33459	0.3701

New model

SOURCE	DF	SS	MS	F-value	PROB>F
MODEL	13	96.8979	7.45369	32.0539	0.0000
ERROR	39	9.069	0.23254		
TOTAL	52	105.967			

RMSE= 0.4822 R2 = 0.9144 PRESS = 16.38105
PRC = 0.2895 LOF= 0.69 R2adj = 0.8859

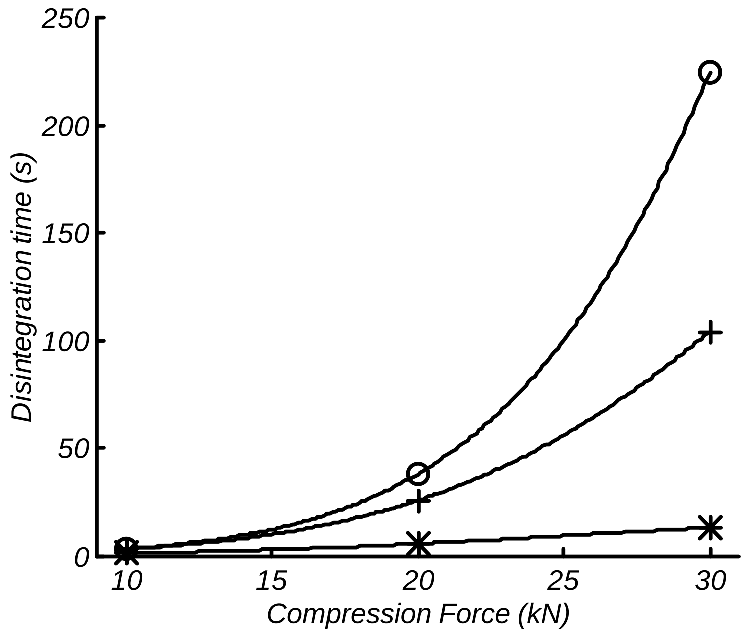

Figure 2: Prediction of the disintegration time of mannitol MCC tablets as a function of the amount of MCC and the compression force. (MCC: o=65%, +=75%, ✳=90%; HPC 3%, granulation time 5 min., moisture content in granulation 4%, water at its medium level).

model (Table 6) has a lower R^2_{adj}, but the PRC and PRESS values improved and it shows no lack of fit.

The amount of MCC has a reducing effect on the disintegration time. Higher compression forces give tablets with shorter disintegration time. The effect of the other variables depends on the level of MCC. Figure 2 shows the disintegration time as a function of compression force and amount of MCC. High levels of MCC give tablets that disintegrate fast as do tablets compressed at 10kN. At a low MCC amount, the effects of compression force, amount of water and moisture in the granules are higher than at high levels of MCC.

Other tablet properties

Table 6 shows models for the ejection force and crushing strength of mannitol MCC tablets. A logarithmic transformation was also used for the crushing strength of the tablets to correct for the heteroscedastic variance structure. MCC has to be below 80% and the compression force must exceed 15 kN to obtain tablets with crushing strengths of at least 40 N. Figure 3A shows the crushing strength as a function of MCC and compression force.For the ejection force of the tablets four observations (exp. 12, 13, 18 and 19; see Table 4) were selected as outliers. Figure 3B shows an obvious effect of the amount of MCC and compression force on the ejection force. When more water is added, the ejection force decreases. For all tablet properties the RMPRESS values are of comparable size to the RMSE and the experimental error (s). At the end of Table 6, indications are given for the tablet properties of the

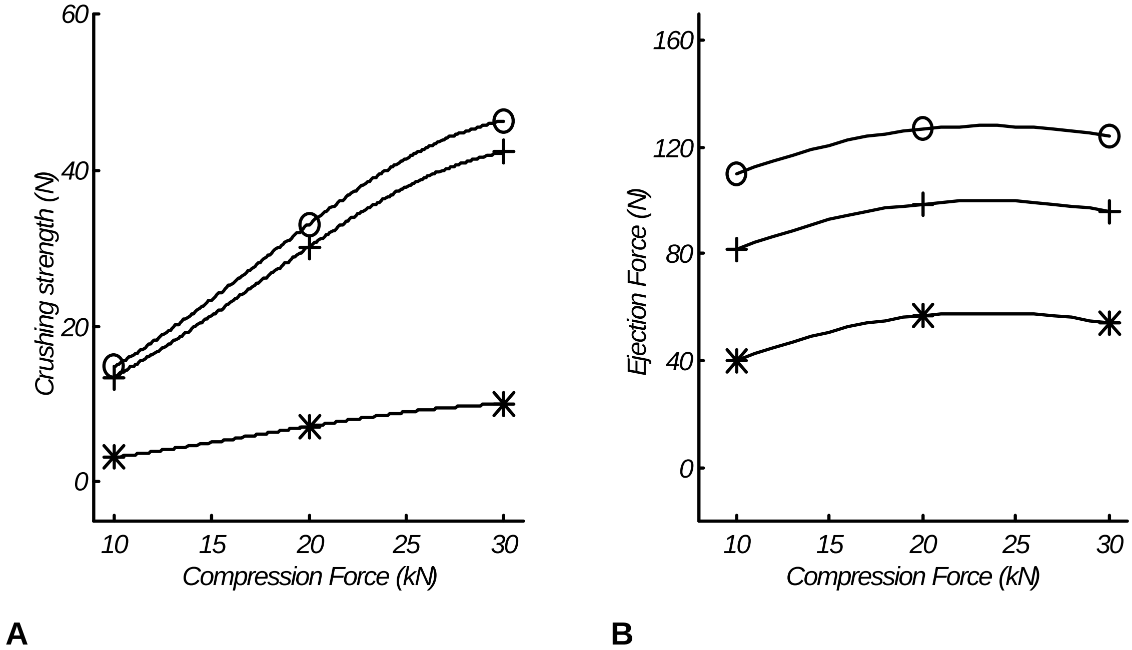

Figure 3: Prediction of the crushing strength (A) and the Ejection force (B) of mannitol MCC tablets as a function of the amount of MCC and the compression force. (MCC: o=65%, +=75%, ✳=90%; HPC 3%, granulation time 5 min., moisture content in granulation 4%, water at its medium level).

experiments with bad compressibilities (t1, 10kN; t2, 30kN). Although the models are extrapolating, they show that the tablets would be very weak and disintegrate fast.

Granule properties

The granule properties were also modelled on the process and composition variables. The compression force and the moisture content in the granules are process variables for the tableting step and are not taken into account for the modelling of the granule properties. Table 7 shows mathematical models constructed to describe the granule responses.

The median granule size is calculated from particle size distribution measurements. Only linear terms of the amount of water and concentration of the binder are used in this model. Both terms have a large positive effect on the response, so the median granule size increases with increasing amounts of water and concentration of binder. With this simple model the data is fitted well and predictions are also good. The percentage of fines indicates the material that has not been granulated or is segregated during handling. The highest percentage can be found at low levels of water and HPC. The number of fines decreases when more water or HPC is added. However when both are high, the percentage of fines increases again. For the specific volumes poured and tapped the same variables are important in the models. The highest specific volumes are obtained at a medium level of MCC and a low amount of water. The flow through a funnel with an orifice of 4.5 mm diameter is modelled with a full quadratic model. A strong curvature of the

Table 7: Final models for median granule diameter, % fines, specific volumes poured and tapped and flow of mannitol MCC granulations. Outliers, R^2, and lack of fit probability are given. Further model parameters are given with their significance (* p<0.05, ** p<0.01, *** p<0.001), and RMSE, error of reproduction (s) and RMPRESS values.

Response	Median granule size (µm)		Fines (%)		Vol. $_{Poured}$ (ml.g^{-1})		Vol. $_{Tapped}$ (ml.g^{-1})		Flow (g.s^{-1})	
Outliers	-		-		-		-		-	
R^2	0.86		0.71		0.76		0.75		0.88	
p(Lack of fit)	0.88		0.37		0.77		0.76		0.73	
Intercept	353.58		2.18		1.65		1.50		1.079	
MCC					-0.0199		-0.013		-0.009	
time			-0.41	*	-0.018		-0.017		0.007	
HPC	64.2	***	-0.37	**	-0.070	**	-0.047	**	-0.043	***
water	156.8	***	-1.06	***	-0.051	**	-0.022		-0.103	***
MCC^2					-0.102	***	-0.097	***	0.094	***
$time^2$					0.056	*	0.054	**	-0.039	*
HPC^2					0.024	*	0.016			
$water^2$			1.02	***	0.057	**	0.042	*	-0.046	**
MCC*time									0.024	*
MCC*HPC									-0.025	**
time*water			0.66	*						
HPC*water			1.30	***					-0.031	*
RMSE	55		0.92		0.08		0.07		0.052	
s	71		0.66		0.09		0.08		0.053	
RMPRESS	57		1.02		0.09		0.075		0.062	

flow in the MCC direction is observed. The lowest flow is reached at medium levels of MCC with large amounts of HPC and water.

Multi criteria optimisation

Crushing strength, disintegration time and ejection force of the tablets are examined simultaneously. Overlay contour plots of the tablet responses are given in Figure 4. Each subplot shows the crushing strength, disintegration time and ejection force of the tablets dependent on compression force and MCC.In the horizontal direction, water is varied from 450 to 550 ml and in the vertical direction the moisture in the granules is varied from 3 to 5%. The gray part of the plots have acceptable values for all tablet responses: crushing strength above 40 N, disintegration times below 300 seconds and ejection forces below 120 N. In each constrained plot (because of the MCC water relation) the upper left corner gives tablets that are too soft, the lower left corner gives ejection forces higher than 120 N and the lower right corner gives tablets with long disintegration times. HPC is set at 3% and the granulation time at 5 minutes.

To result in good mannitol/MCC tablets, MCC should be between 65 and 80%, water should be about 500 g or higher, dependent on the MCC amount and compression force must be about 25 kN. When the granulations contains more than

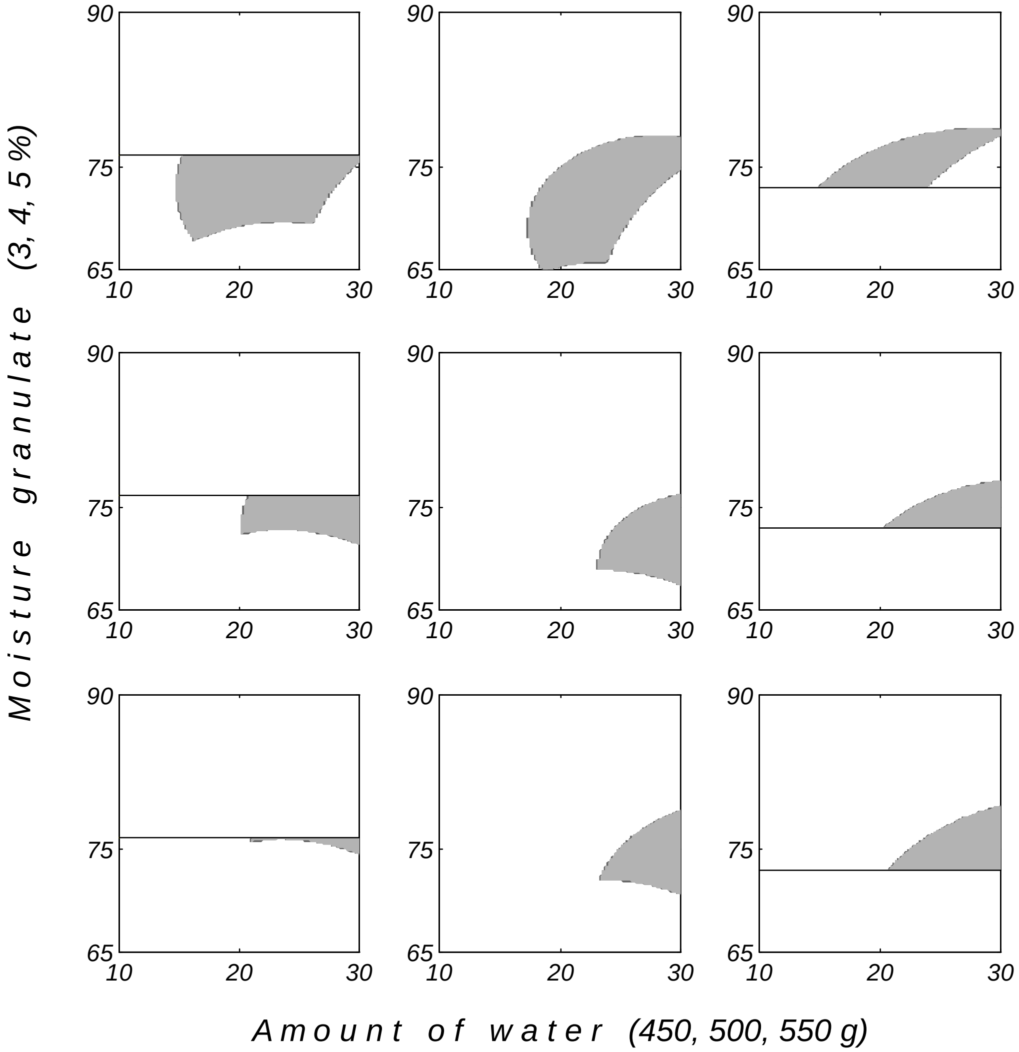

Figure 4: Overlay contour plots of crushing strength, disintegration time and ejection force. In each plot compression force (10, 20, 30kN) and MCC (65, 75, 90%) are varied. Horizontally water changes from 450 to 550 ml and vertically moisture in the granulation (3, 4, 5%). The dark area represents tablets with crushing strengths > 40N, disintegration times < 5 minutes and ejection force < 120N (HPC 3%, granulation time 5 min.).

5% moisture the tablets become stronger and a compression force of 20 kN satisfies. This also causes a lower ejection force, but the disintegration time increases. More compression force or less MCC gives stronger tablets. Table 8 shows predicted tablet properties for some settings of process variables. More HPC decreases the ejection force, but if enough water is added during granulation, HPC can be kept low.

Table 8: Predicted properties of mannitol MCC tablets at some settings of the composition and process variables

MCC (%)	HPC (%)	Moisture (%)	Water (g)	Fup (kN)	Time (min.)	Crushing strength(N)	Disintegr. time (s)	Ejection force (N)
75	3	5	450	20	5	51	74	102
75	3	5	450	25	5	59	160	103
70	3	5	500	20	5	48	134	100
75	3	5	500	25	5	45	144	93
75	3	5	550	20	5	43	106	81
70	3	4	500	25	5	46	95	110
75	3	4	550	25	5	41	83	91
75	3	3	550	25	5	43	86	100

Conclusion

Mixtures of MCC and mannitol in tablets can be used as a good alternative to classical filler excipients. The amounts of MCC, HPC and water strongly affect tablet properties as do compression force and moisture of the granulation. Granulation time hardly affects tablet properties. The amount of HPC does not influence the crushing strength and ejection force of the tablets. The combination of MCC and mannitol gives tablets with short disintegration times and sufficient strength. For tablets with crushing strengths more than 40 N, disintegration times less than 300 seconds and ejection forces less than 120 N, the amount of MCC should be between 65 and 80%, the compression force must be 25 kN and the amount of water should be at least 500 g, dependent on the MCC amount. When the moisture content in the granulation is 5%, a compression force of 20 kN appears adequate.

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